

**REMARKS**

Claim 14 is pending in the subject application.

The Examiner rejected claim 14 under 35 U.S.C. § 112, first paragraph as allegedly being non-enabling for the reasons set forth in the office action. In particular, the Examiner focused on four of the eight factors set forth in *In re Wands* and contended that those skilled in the art could not make and use the full scope of the invention without undue experimentation. Applicants traverse this rejection.

Claim 14 of the subject application recites “a method for preventing an influenza virus infection in a warm-blooded animal, which comprises administering to such animal a therapeutically effective amount of a composition comprising an agent selected from ambroxol, bromhexin, the pharmaceutically acceptable salts of ambroxol or bromhexin and combinations thereof, and an additive.” The subject specification states that ambroxol and/or bromhexin has an anti-oxidative effect and can serve as a sputum-dissolving agent capable of promoting the release of pulmonary surfactants (PS) (see page 4, line 26 to page 5, line 1). As also noted in the specification of the invention, pulmonary surfactants in the lung are part of the “principal immunological defensive system for preventing any invasion of viruses into cells and more specifically, the induction of local secretion of immunoglobulin Iga and IgG is closely related to the protection from the influenza virus infection (Refs. 11-13)” (see page 2, lines 16-26). The specification also states that “ambroxol has such pharmacological functions as the control of mucus on the adenocyte of the respiratory tract and the promotion of the PS-production (Ref. 15)” (see page 3, lines 24-26).

**(I) The nature of the invention, state and predictability of the art, and relative skill to those in the art**

The Examiner refers to Yang et al., Eur. Respir. J. 2002, 19:952-958 (“Yang et al.”); Harper et al., Prevention and Control of Influenza, May 28, 2004 53 (RR-6):1-40 (“Harper et al.”); and WO 95/07103 to Mitra et al. (“Mitra et al.”) “[a]s illustrative of the state of the art.” The Examiner asserts that the “references plainly demonstrate that prevention of influenza is an art recognized hurdle. The references also demonstrate that influenza can be treated, proliferation can be suppressed, and the incidence thereof can be reduced.” The Examiner states that “there is nothing in the art that supports prevention of infection of the flu virus.” Applicants disagree.

Yang et al. relates to the suppression of influenza-virus proliferation in the mouse airway by increasing antiviral factor levels. Yang states: "Ambroxol stimulated the release of suppressors of influenza-virus multiplication, such as pulmonary surfactant, mucus protease inhibitor, immunoglobulin (Ig)-A and IgG" (see Abstract, page 925 of Yang et al.). Yang et al. also states that "[a]lthough ambroxol had several negative effects on the host defense system, overall it strikingly increased the concentrations of suppressors of influenza-virus multiplication in the airway" (see Abstract, page 925 of Yang et al.). Yang et al. also states that "ambroxol might possibly be applied clinically for the treatment or prevention of influenza-virus infection in humans" (see page 958, first full paragraph at top left column of Yang et al.). However, nothing in Yang et al. states that ambroxol cannot be used to prevent infection of the flu virus as asserted by the Examiner.

Harper et al. relates to prevention and control of influenza. Harper et al. also discusses the effectiveness of vaccines including its effect on different populations (see pages 7 and 10-13 of Harper et al.). Harper describes immunoprophylaxis using inactivated (i.e., killed virus) influenza vaccine and live, attenuated influenza vaccine (see page 7 under "Options for Controlling Influenza" of Harper et al.). Harper et al. also describes using antiviral agents as an adjunct to influenza vaccine for controlling and preventing influenza (see page 41 to 57 under "Recommendations for Using Antiviral Agents for Influenza" of Harper et al.). However, nothing in Harper et al. states that ambroxol cannot be used to prevent infection of the flu virus as asserted by the Examiner.

Mitra et al. relates to compositions useful for treatment of cold, cold-like, and or flu symptoms. Mitra et al. describes optional ingredients that include inter alia expectorants including bromhexine and ambroxol (see page 5, lines 28-30 of Mitra et al.). However, nothing in Mitra et al. states that ambroxol cannot be used to prevent infection of the flu virus as asserted by the Examiner.

In summary, none of the state of the art references cited by the Examiner, i.e., Yang et al., Harper et al., and Mitra et al., supports the Examiner's position regarding the prevention of the flu virus.

Applicants refer to an article to Olevieri et al., "Ambroxol for the Prevention of Chronic Bronchitis Exacerbations: Long-Term Multicenter Trial," *Respiration* 51: Suppl. 1, pp. 42-52 (1987) ("Olevieri et al.") (included with the Information Disclosure Statement filed concurrently herewith). Olevieri et al. relates to a 6-month study to determine if prophylactic administration of ambroxol was more effective than a placebo in preventing chronic

bronchitis. Olivieri et al. states that “ambroxol was well tolerated and ... it appears like a drug of choice for pharmacological prophylaxis of chronic bronchitis” (see Abstract, page 42 of Olivieri et al.). Olivieri et al. further describes the factors that contribute to the pharmacological activity of ambroxol including enhanced production of surfactants. Thus, Olivieri et al. indicates that it was known in the art at the time of filing the subject application to use ambroxol as a prophylactic for treating chronic bronchitis. Also as discussed above, it was known in the art at the time of filing the subject application that enhanced production of pulmonary surfactants are useful for preventing any invasion of viruses into cells such as those causing chronic bronchitis.

“The specification need not disclose what is well-known to those skilled in the art and preferably omits that which is well-known to those skilled and already available to the public” (see MPEP § 2164.05(a)).

For the reasons discussed above, the state of the art at the time the subject invention was filed supports the use of ambroxol to prevent infection of the flu virus. Therefore, claim 14 of the subject application which recites “a method for preventing an influenza virus infection in a warm-blooded animal, which comprises administering to such animal a therapeutically effective amount of a composition comprising an agent selected from ambroxol, bromhexin, the pharmaceutically acceptable salts of ambroxol or bromhexine and combinations thereof, and an additive” is predictable.

## **(2) The breadth of the claims**

With regard to the breadth of the claims, the Examiner merely states that “[t]he claim is broad.” Applicants disagree.

Claim 14 of the subject application does not recite a genus of diseases or even a large number of specific diseases. Rather, claim 14 recites “a method for preventing an influenza virus infection” using “ambroxol or bromhexin and combinations thereof, and an additive.” Such method is disclosed in the specification and within the skill of those in the art for the reasons discussed in Section (1) above.

“As concerns the breadth of a claim relative to enablement, the only relevant concern should be whether the scope of the enablement provided to one skilled in the art by the disclosure is commensurate with the scope of the protection sought by the claims” (see MPEP § 2164.08).

Because the scope of claim 14 is commensurate with the scope of the disclosure, claim 14 is not overly broad.

**(3) The amount of direction or guidance provided and the presence or absence of working examples**

With regard to the direction or guidance, the Examiner states that “[t]he specification provides no direction for determining the particular administration regimes (dosage, timing, administration routes, etc.) necessary to prevent an influenza virus infection in warm-blooded animals.” With regard to working examples, the Examiner states that “[t]he working examples are limited to treating and inhibiting proliferation of the influenza virus. Thus, the applicant at best has provided specific direction or guidance only for treating and inhibiting proliferation of an influenza virus infection.” The Examiner contends that “[n]o reasonably specific guidance is provided concerning useful preventive protocols for an influenza infection.” Applicants disagree.

As noted above in Section (1), it was known in the art at the time of filing the subject application that ambroxol could be used to prevent chronic bronchitis based in part on the production of pulmonary surfactants. As described in the subject application, ambroxol increases the production of pulmonary surfactants, and pulmonary surfactants are the “principal immunological defensive system for preventing any invasion of viruses into cells.” Thus, one of skill in the art – in view of the subject specification and the state of the art – would be able to use ambroxol to prevent influenza infection.

“The specification need not contain an example if the invention is otherwise disclosed in such manner that one skilled in the art will be able to practice it without an undue amount of experimentation” (see MPEP § 2164.02). “The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art” (see MPEP § 2164.03).

Ambroxol is known to be useful for prevention of chronic bronchitis based in part on the increased production of pulmonary surfactants. And increased production of pulmonary surfactant is known to be an immunological defensive system for preventing invasion of viruses into cells. Therefore, one of skill in the art would have sufficient guidance to use ambroxol to prevent in influenza virus infection without undue experimentation.

**(4) The quantity of experimentation necessary**

With regard to the quantity of experimentation, the Examiner refers to the art-recognized hurdle discussed in Section (1) above and asserts that "in the absence of experimental evidence commensurate in scope with the claims, the skilled artisan would not accept the assertion that the instantly claimed method could be predictably used to prevent an influenza virus infection as inferred in the claims and contemplated by the specification."

Applicants disagree. For the reasons discussed in Sections (1) - (3) above, a skilled artisan would appreciate that claim 14 is commensurate in scope with the specification, and claim 14 could be practiced without undue experimentation.

In view of the above, Applicants submit that claim 14 is enabled, and request that the rejection of claim 14 under 35 U.S.C. § 112, first paragraph be withdrawn.

**CONCLUSION**

Applicants respectfully request prompt consideration of the pending claims and early allowance of the application. No additional fee is believed due. However, if any additional fee is due, the Examiner is authorized to charge the fee to Applicants' Deposit Account No. 02-2955.

If a telephonic or personal interview is deemed necessary to expedite the examination of the instant application, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

Respectfully submitted,

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